<table>
<thead>
<tr>
<th><strong>Short title</strong></th>
<th>GIMEMA ALL 0904 PROTOCOL</th>
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<tbody>
<tr>
<td><strong>Full study title</strong></td>
<td>Intensification of post-remissional treatment of high-risk acute lymphoblastic leukemia in adults and minimal residual disease monitoring</td>
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<tr>
<td><strong>Study code / number</strong></td>
<td>EudraCT number 2004-001738-17</td>
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<tr>
<td><strong>Name of the study group</strong></td>
<td>GIMEMA</td>
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<td><strong>Study type</strong></td>
<td>Prospective, multicentric, not randomized.</td>
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<td><strong>Sample size</strong></td>
<td>A minimum of 113 patients will be enrolled.</td>
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<td><strong>Disease</strong></td>
<td>Acute lymphoblastic leukemia (ALL)</td>
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<td><strong>Stage</strong></td>
<td>De novo</td>
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<tr>
<td><strong>Age</strong></td>
<td>( \geq 15 \leq 60 ) yrs</td>
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| **Aims** | 1. Evaluation of the role of intensification in post-remissionsal therapy using transplant procedures in order to improve the disease-free survival (DFS) at one year in high risk patients.  
2. In resistant patients, without progressive disease, after 2nd (blasts \( \geq 20\% \)) or 3rd (blasts >5) induction cycle: evaluation of the activity of HAM as 2nd line treatment, in terms of CR achievement.  
3. Feasibility of the monitoring of MRD in high and standard risk patients.  
4. Prognostic impact of MRD in high and standard risk patients.  
5. Overall survival from diagnosis. |
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| **Inclusion Criteria** |  
- Acute lymphoblastic leukemia (pro-B, common, pre-B, early T, thymic T, mature T)  
- Age \( \geq 15 \leq 60 \) years  
- Written informed consent |
| **Exclusion Criteria** |  
- Cytostatic and prednisone pre-treatment  
- Mature B-ALL (FAB L3, slg+, TdT-)  
- Severe comorbidity or leukemia associated complications |
### Study Design / Treatment overview

<table>
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<tr>
<th><strong>• Severe psychiatric illness which may compromise cooperation of the patient</strong></th>
<th><strong>Concomitant malignancy</strong></th>
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</table>

All patients receive uniform **induction therapy** (pre-phase, induction phase). After achievement of CR treatment, **stratification** according to risk factors takes place.

**Standard risk patients:**
Consolidation: 2 cycles with HDARA-C and VP-16
Continuous maintenance with MTX/6MP and re-induction with alternating cycles of VCR/PDN/CTX and VCD/PDN/DNR for 3 years from CR.

**High risk patients:**
Consolidation: HAM schedule (HDARA-C and Mitoxantrone) plus G-CSF.
**Eligible patients in CR with an HLA+ sibling donor** will undergo the allograft immediately after recovery from HAM and not later than 3 months.
**Patients in CR without an HLA+ sibling donor** will undergo transplant from an “alternative” donor, according to the policy of the Center.
**Patients NOT eligible or who do not have an available donor** will be submitted to leukaphereses to collect a minimum of $2 \times 10^6$/kg CD34+ cells after HAM.

**Ph+ or BCR-ABL+ patients:** after achievement of CR and HAM consolidation, patients are treated according to a separate protocol (GIMEMA ALL 0201) with Imatinib alone.

**Prophylaxis and CNS disease treatment**

**During induction:**
**Prophylaxis:** MTX IT on day previous to 2nd or 3rd cycle of DNR (d +21 and d +35).
**CNS disease:** use the “triple” combination (metil-prednisolone, ARA-C, MTX) twice a week until liquor is negative, then once a week for two weeks.

**Standard risk patients:**
After consolidation therapy, patients in CR will receive a combined treatment of chemotherapy and radiotherapy, according to the following scheme:
**MTX-IR:** twice a week for 4 times (for a total number of 6 administrations).
**X-ray (RT) on the central nervous system (CNS):** at a daily dose of 200 cGY for 5 days a week (total dose of 1800 cGY).
**Maintenance course**
Therapeutic rachicentesis (MTX IR) once a month for 12 months.

**High risk patients**
Patients undergoing an **autograft** will receive a monthly therapeutic lumbar puncture with MTX 15 mg for one year, starting one month after complete hematological recovery. Patients undergoing an **allogeneic transplantation** will be treated according to the Investigator’s opinion (according to the Center).

**Stratification according to risk factors**

1. **Standard risk (SR)** (all the following parameters have to be fulfilled):
   - WBC ≤50,000 at diagnosis
   - Response to pre-treatment with steroids (reduction of blast >75%)
   - CR at the end of the induction therapy
   - Cytogenetics at diagnosis: absence of the following translocations: t(9;22), t(4;11), t(1;19).

2. **High risk (HR)**
   - Patients not responding to the pre-treatment with steroids, or
   - WBC >50,000 at diagnosis, or
   - Resistant patients after 2nd (bone marrow blasts ≥20%) or 3rd cycle (bone marrow blasts >5%) induction cycle, or
   - Cytogenetics: t(9;22), t(4;11), t(1;19).
### Overview
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<th>Central diagnostics</th>
<th>Morphology</th>
<th>Immunophenotyping</th>
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<tbody>
<tr>
<td>Cytogenetics</td>
<td></td>
<td>Molecular genetics</td>
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<tr>
<td>MRD</td>
<td></td>
<td>Other</td>
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### Biometrics

<table>
<thead>
<tr>
<th>Paola Fazi, MD</th>
<th>Simona Iacobelli, Biostatistician</th>
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<tbody>
<tr>
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### Sponsors
GIMEMA Foundation

### Seal of approval
GIMEMA
Pre-phase

Induction phase cycle 1 and 2

CR/PR → no → Progression → yes → OFF

yes

Induction phase cycle 3

CR → no

MRD-1

CNS RT

MRD-2

Risk stratification

Standard

consolidation

High

AraC+Ida

Ph+

yes

ALL 0201

Imatinib +/- BMT

MRD-3

Autograft+maintenance

BMT